AD_____

Award Number: DAMD17-03-1-0681

TITLE: Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor Ligands for ER+ Tumor Imaging

PRINCIPAL INVESTIGATOR: Nathan C. Ackroyd
John A. Katzenellenbogen, Ph.D.

CONTRACTING ORGANIZATION: University of Illinois
Champaign, IL 61820-6200

REPORT DATE: October 2005

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-10-2005	Annual Summary	5 Sep 2003 – 4 Sep 2005

4. TITLE AND SUBTITLE
Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor Ligands for ER+ Tumor Imaging

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-03-1-0681

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Nathan C. Ackroyd
John A. Katzenellenbogen, Ph.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Illinois
Champaign, IL 61820-6200

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
Original contains colored plates: ALL DTIC reproductions will be in black and white.

14. ABSTRACT

A class of breast tumors, known as ER+, contains significant concentrations of ER which functions to regulate cell growth, and mediate the action of estrogen antagonists. There is a need for the development non-invasive and reliable methods for the determination of tumor ER concentration in the identification of patients predicted to respond to hormone therapy. It has been shown that tumor ER concentration can be determined by imaging, using 18F-labeled ER selective ligands, and that the ER concentrations determined by imaging correlate well with those determined by immunoassay methods on surgical biopsies. Because of the short half-life of fluorine-18, this method is costly, with low availability. Thus, the development of an effective ER imaging agent that is of low cost and widespread availability might eliminate the need for tumor biopsy in the treatment selection for breast cancer patients. We propose the development of radiopharmaceutical imaging agents labeled with 99mTc, which is available at most hospitals at a relatively low cost, as a 99Mo/99mTc generator. Studies conducted in this laboratory suggest that an integrated organometallic design in which technetium bonded to carbon forms a part of the core structure will display the stability, as well the requisite affinity to ER.

15. SUBJECT TERMS
Breast Cancer

16. SECURITY CLASSIFICATION OF:				18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	12	

Table of Contents

Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor (ER) Ligands for ER+ Tumor Imaging

Nathan C. Ackroyd, University of Illinois, Urbana-Champaign, 600 S. Mathews Ave, Urbana, IL, 61801.

Introduction

It is known that many breast tumors contain significant concentrations of ER. In these tumors, known as ER+ tumors, the role of ER is to regulate cell growth, but it can also function to mediate the anti-proliferative effects of estrogen antagonists, such as tamoxifen. It has been shown that ER concentration correlates well with the efficacy of anti-estrogen use in hormone therapy. Tumors with low ER concentration (i.e., ER- tumors) do not respond well to hormone therapy. As a result, chemotherapy is often used instead of hormone therapy, in spite of the high morbidity associated with its use, because chemotherapy is known to be effective in both ER+ and ER- tumors. Unfortunately, roughly half of patients that are successfully treated with chemotherapy could have been treated equally well with hormone therapy and thereby avoided the deleterious side effects of chemotherapy, provided that a reliable means could be used to identify those patients that would respond to hormone therapy. Thus, there is a great need for the development of a non-invasive and reliable method for the determination of ER concentration in tumors that would allow identification of breast cancer patients having ER+ tumors that are likely to respond well to hormone therapy, so that these patients could be spared the side effects of chemotherapy. It has been shown that the ER concentration in breast tumors can be determined by imaging, using ER selective radiopharmaceutical imaging agents, and that the ER concentrations determined by imaging correlate well with those determined by binding or immunoassay methods on surgical biopsies. Currently, the most effective ER imaging agent is a fluorine-18 labeled estrogen. However, because of the short half-life of this radionuclide, this agent is very expensive and is not widely available. Thus, the development of an effective ER imaging agent that is of low cost and widespread availability might eliminate the need for tumor biopsy to determine whether a patient is a good candidate for hormone therapy. We have proposed the development of a radiopharmaceutical imaging agent labeled with ^{99m}Tc, which exhibits a high binding affinity to ER, has high *in vivo* stability, and functions effectively *in vivo* for imaging ER levels in breast tumors. Imaging agents labeled with ^{99m}Tc would be available at most hospitals and at a relatively low cost, because ^{99m}Tc is widely available from a ^{99}Mo/^{99m}Tc generator. Previous studies of technetium–99m labeled ER ligands for use as imaging agents have suffered from several problems. Inorganic chelates of ^{99m}Tc demonstrated molecular instability under biological conditions; also, the large size of many Tc complexes interferes with cellular uptake. Studies conducted in this laboratory suggest that an integrated organometallic design in which technetium bonded to carbon forms a part of the core structure will display the needed stability, as well the potential for high binding affinity to ER. While significant advances have been made, major improvements in radiolabeling techniques and structural design are still needed before an imaging agent using ^{99m}Tc will be effective as a diagnostic tool to identify tumors that will respond to hormone therapy. The structural design motif under investigation is based upon previous work in our laboratory, as well as molecular modeling with comparison to the morphology of the native ER ligand, estradiol.

Body of Report

I. Training

In the past year I have attended the International Symposium on Radiopharmaceutical Chemistry in Iowa City, Iowa, June 24-28, 2005. I have also attended various organic-chemistry, organometallic-chemistry, and chemical-biology seminars presented by visiting professors and UIUC students.

II. Research

The overall objective of this proposal is to develop a compound bearing a ^{99m}Tc label that exhibits both a high relative binding affinity to ER, has good *in vivo* stability, and functions effectively as an imaging agent for ER in breast tumors. Ultimately, we hope that this compound could be used to image ER+ tumors in a manner that would provide information useful for the selection of the optimal therapy for a breast cancer patient. This aim has been divided into four tasks, which make up the approved Statement of Work.

Task A: (Months 1-18, July 1, 2003 – December 31, 2004)

- Begin model studies for synthesis of compound **PyCR (II)**.
- Begin synthesis of **ACR (IV)**.

Task B: (Months 13-30, August 1, 2004 – December 31, 2005)

- Execute synthesis of **PyCR (II)**, and determine relative binding affinity.
- Execute synthesis of **PIRB (VI)** analogs and determine relative binding affinity.

Task C: (Months 25-36, July 1, 2005 – June 30, 2006)

- Execute synthesis of analogs of **PyCR (II)**, with various combinations of alkyl and aryl substitution on the central cyclopentadienyl ring.
- Execute synthesis of **PIRM (VII)** analogs and determine relative binding affinity.
- Execute synthesis of the **ACR** (**IV)**, and determine relative binding affinity.
- Develop synthesis of **CBRN (VIII)**, and determine relative binding affinity.

Task D: (Months 12-36, July 1, 2004 – June 30, 2006)

- We will develop methods of radiolabeling using ^{94m}Tc in place of Re and evaluate the *in vivo* tissue distribution of all labeled compounds with promising *in vitro* properties. (To be done through our long-standing collaboration with Professor Michael Welch of the Mallinckrodt Institute of Radiology at Washington University Medical School)

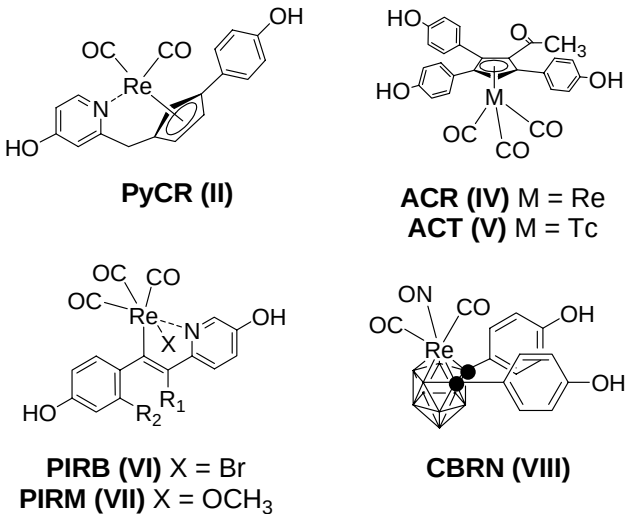


Figure 1. ER Ligand Targets

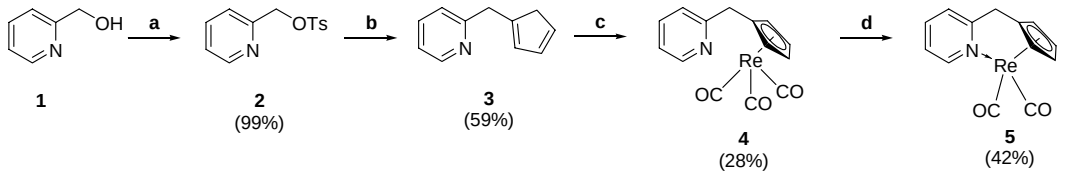
The second twelve months of award coverage described in the approved Statement of Work includes the completion of two steps listed as Task A, the majority of Task B, and initial progress on Task C. Progress in Task A, though covered by this report, includes work described in annual report I.

Task A Step 1

The model study for the synthesis of $\eta^1\eta^5$-complex PyCR **II** has been completed with the synthesis of η^1,η^5-pyridylmethylcyclopentadienyl rhenium(I) dicarbonyl (**5**), which forms the core of the phenol substituted PyCR **II**. Production of **5** proceeds in four steps from commercially available 2-pyridylmethanol **(1)**, as shown in

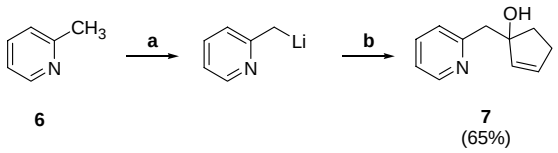
Scheme 1. The essential pyridine to rhenium cyclization occurs via photo-irradiation under inert atmosphere to provide the desired rhenium dicarbonyl complex. Alternatively, the production of the (pyridylmethyl)cyclopentadiene (**3**) can be accomplished in a one-pot procedure using the lithium anion of picoline (**6**) and cyclopentenone, as shown in Scheme 2, followed by dehydration.

Scheme 1



(a) TsCl, KOH, THF, RT, overnight. (b) NaCp, THF, -78 °C. (c) n-BuLi, $[ReBr(THF)_2(CO)_3]_2$, RT, 20 min. (d) hν, 300 nm. 90 min.

Scheme 2

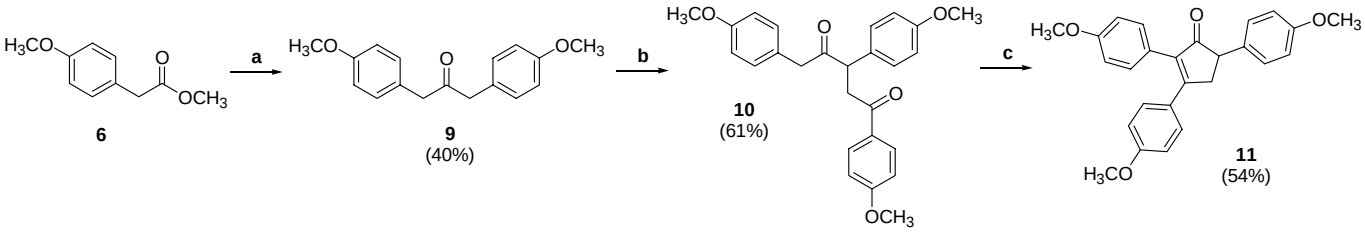


(a) *n*-BuLi, THF, -78 °C, 20 min. (b) 2-cyclopentenone, 20 min.

Task A Step 2

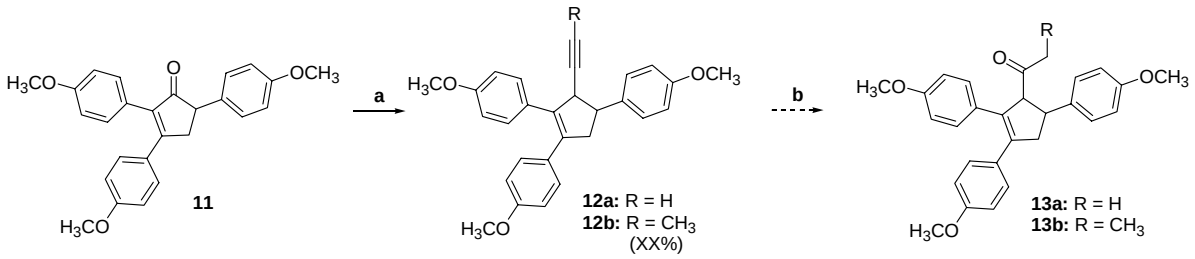
The synthesis of 2,3,5-tris-(4-methoxyphenyl)cyclopentenone (**11**), as shown in Scheme 3, has been completed in three steps, starting from commercially available methyl 4-methoxyphenylacetate (**8**). Several methods have been investigated for the addition of a fourth substituent to the central pentacycle, including nucleophilic addition of organometallic reagents, addition of electrophiles to the cyclopentadiene derived from **11**, Wittig and titanium mediated olefination, followed by hydride transfer, and zirconocene-mediated cyclopentenone formation. Ultimately, the nucleophilic addition of 1-propynylmagnesium bromide to the carbonyl of enone **11** provided the tetra-substituted 2,3,5-tris-(4-methoxyphenyl)-1-propynylcyclopentadiene (**12b**), as shown in Scheme 4. Initial attempts to hydrate the triple bond of alkyne **12b** using transition metal catalysis have thus far failed to provide the desired ketone **13b**, although additional trials with be undertaken as part of Task C.

Scheme 3



(a) i. LDA, ether, -78 °C, 20 h. ii. AcOH, HCl, reflux, 5h. (b) i. LDA,THF, -78 ^{0}C, 1 h. ii. 2-bromo-4'-methoxyacetophenone, 1.5 h. c. methanolic KOH, RT, 20 min.

Scheme 4

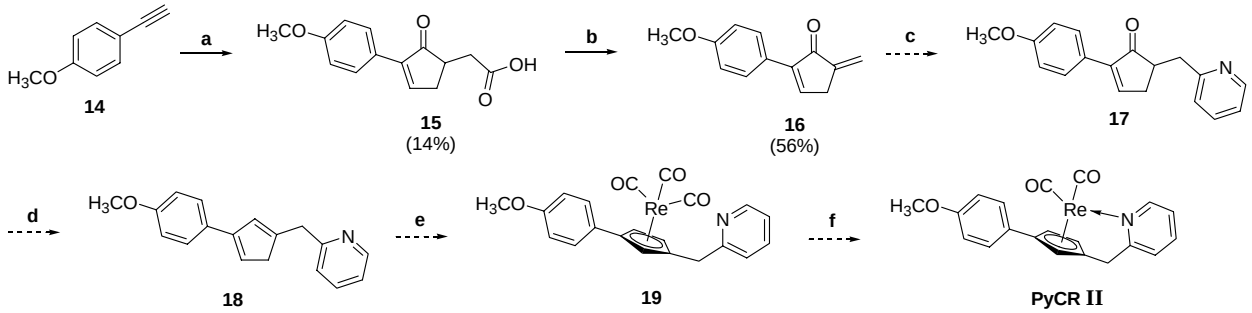


(a) i. TMS-acetylene, *i*-Pr-MgBr, 30 min, 0°C, THF. ii. ethanol. iii. Repeat cycle 6.

Task B Step 1

The completion of the model study in Step 1 of Task A led to attempts to synthesize the phenol substituted **PyCR**. Early routes to a hydroxyphenyl substituted pyridylmethyl cyclopentadiene, described in Annual Report I, shared the reactivity limitations of enone 4, described above. A recent report describes a catalytic intermolecular 2+2+1 cyclization to form cyclopentenones using allyl bromide.[1] This variation on the Puason-Khand Reaction (PKR) does not suffer from the substrate limitations inherent in the PKR, as well as providing the essential methylene in a 1,3 relationship to the protected phenol. Initial cyclization provides the cyclopentenone acid **15**, which eliminates to form cross-conjugated dienone **16** under decarboxylation conditions. Future work includes the conjugate addition of a pyridyl Grignard or cuprate[2] reagent to the more reactive *exo*-enone of **16** to provide the pyridyl enone **17**. Hydride reduction and dehydration to the cyclopentadiene **18**, followed by two coordination steps and deprotection will lead to the $\eta^1\eta^5$-complex **PyCR II**

Scheme 5

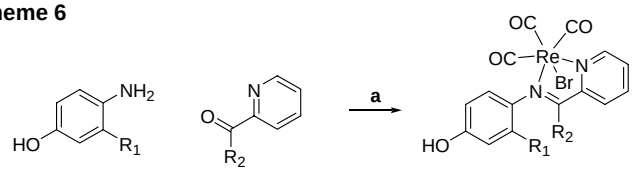


(a) $NiBr_2$, NaI, $AlBr_3$, Fe, CO, acetone, RT, 5h. (b) 2-Mercaptopyridine N-oxide, DCC, $CBrCl_3$, reflux, 5h. (c) Pyridyl cuprate reagent, BF_3•OEt_2. (d) DIBALH, THF, -78° C, 4h. (e) i. n-BuLi, THF, -78° C, 15 min. ii. $[ReBr(THF)_2(CO)_3]_2$, RT, 20 min. (f) hν, 300nm, THF, 90 min.

Task B Step 2

As discussed in Annual Report I, the synthetic ease of imine formation, as well as the strong coordination of the nitrogen of pyridine makes a pyridyl-imine based scaffold attractive for the bidentate portion of a 2+1 ligand system in the production of radio-labeled ER ligands. The anionic monodentate ligand is bromide for the pyridyl-imine rhenium tricarbonyl bromide (**PIRB VI**) system. A nomenclature of PIRB ligands is based on whether a hydroxyl appears on the aniline moiety (A-ring mimic), the pyridine (D-ring mimic), and the identity of substituents R_1, and R_2. As shown in Scheme 6, a variety of commercially available hydroxyaniline derivatives **20-22** were combined with either pyridinecarboxaldehyde **23** or acetylpyridine **24** in refluxing methanol**,** followed by addition of a rhenium tricarbonyl salt formed the monohydroxy rhenium complexes **25a-d**, with the aniline moiety forming the A-ring mimic.

Scheme 6



20: R_1 = H
21: R_1 = CH_3
22: R_1 = Cl

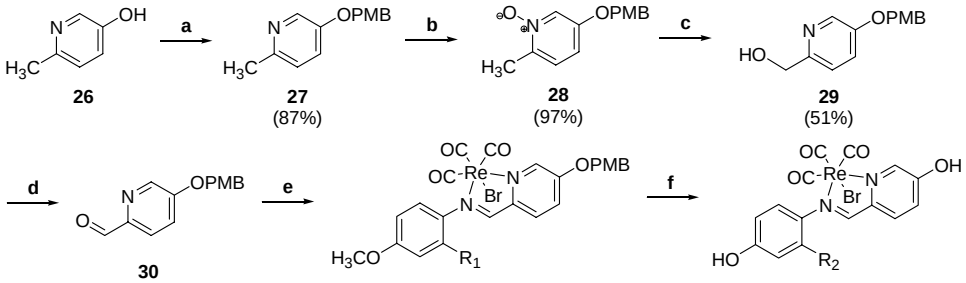
23: R_2 = H
24: R_2 = CH_3

25a, AHH: R_1 = H R_2 = H (XX)%
25b, AMH: R_1 = CH_3 R_2 = H (54)%
25c, ACH: R_1 = Cl R_2 = H (XX)%
25d, AHM: R_1 = H R_2 = CH_3 (75)%

(a) i. methanol, reflux, 2h. ii. $[NEt_3]_2[ReBr_3(CO)_3]$, 5 min.

Synthesis of the dihydroxy complexes begins with the protection of the hydroxypicoline **26**, as the *p*-methoxybenzyl ether **27**. Oxidation to the N-oxide **28** with peroxy acid, with subsequent rearrangement provides the alcohol **29**. Benzylic oxidation yields the aldehyde **30** needed for imine formation. Condensation with anisidine derivatives, followed by addition of the rhenium salt causes the protected rhenium complexes **31a-b** to precipitate from solution. Deprotection with Lewis acid Boron tribromide reveals the dihydroxy complexes **32a-b**.

Scheme 7



26

27 (87%)

28 (97%)

29 (51%)

30 (33%)

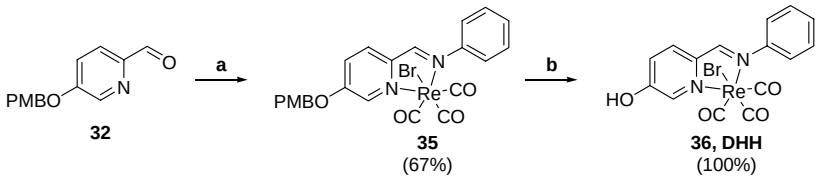
31a: R_1 = H (53%)
31b: R_1 = Cl (85%)

32a, ADHH: R_1 = H (90%)
32b, ADCH: R_1 = Cl (90%)

(a) PMBCl, NaH, THF. (b) mCPBA, $CHCl_3$. (c) i. $(CF_3CO)_2O$, CH_2Cl_2. ii. CH_3OH. (c) MnO_2, CH_2CL_2. (d) i. Anisidine, CH_3OH, reflux. ii. $[NEt_4]_2[ReBr_3(CO)_3]$. (e) BBr_3, CH_2Cl_2, -78° C - RT.

The corollary to monohydroxy **25a**, in which the pyridine moiety forms the A-ring mimic, is formed using the above procedure, starting with protected hydroxy aldehyde **32**, which undergoes condensation with unsubstituted aniline to form rhenium complex **35**. Deprotection reveals the monohydroxy complex **36.**

Scheme 8



32

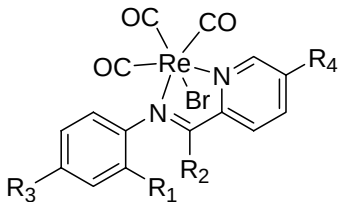
35 (67%)

36, DHH (100%)

(a) i. Aniline, CH_3OH, reflux, 2h. ii. [NEt4]2[ReBr3(CO)3]. (b) BBr_3, CH_2CL_2, -78° C - RT.

For all **PIRB** complexes synthesized, binding affinities relative to estradiol (100%) are listed in Table 1 for both ERα and β. The highest affinity compound thus far is **32a**, **ADHH**. Among mono-hydroxy compounds **25a-d, 36**, substitution in the R_2 position increases binding affinity. This is supported by molecular modeling (Figure 2), which for lead compound **ADHH (32a)**, chloro mono-hydroxy **ACH** (**25c)**, and bis-hydroxy **ADCH (32b),** show free space in the receptor opposite the imine carbon. This suggests that a number of bis-hydroxy keto-imines be synthesized in order to improve binding affinity. Substitution in the R_1 position has mixed effects, raising binding affinity for **ACH (25c)**, but lowering binding affinity for **AMH (25b)**, relative to H-substituted **AHH (25a)**. This effect cannot be explained by the difference in halogen versus alkyl, as the substitution of a chloride, which has previously improved binding affinity, lowered it for **ADCH (32b)** versus **ADHH (32a)**.

Table 1. PIRB Relative Binding Affinity (E2 = 100%)



	R_1	R_2	R_3	R_4	ERα	ERβ
25a, AHH	H	H	OH	H	0.015%	0.011%
25b, AMH	CH_3	H	OH	H	<0.005%	<0.005%
25c, ACH	Cl	H	OH	H	0.327%	0.0185%
25d, AHM	H	CH_3	OH	H	0.071%	0.055%
32a, ADHH	H	H	OH	OH	0.271%	2.29%
32b, ADCH	Cl	H	OH	OH	<0.01%	0.01%
36, DHH	H	H	H	OH	<0.01%	0.015%

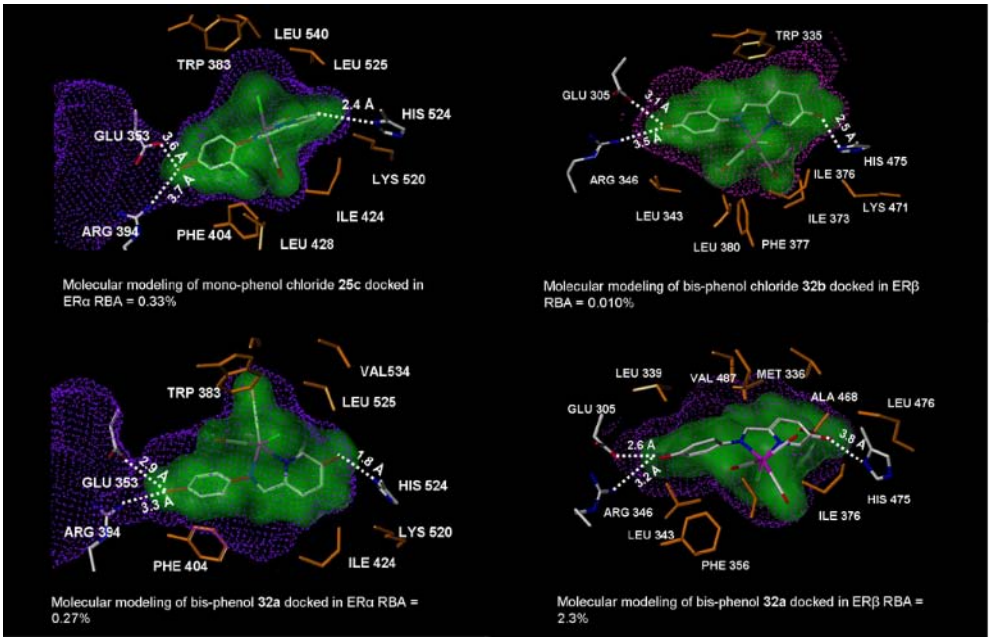
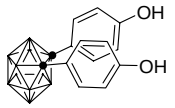


Figure 2. Molecular Modeling of Selected PIRB Ligands

Task B Step 3

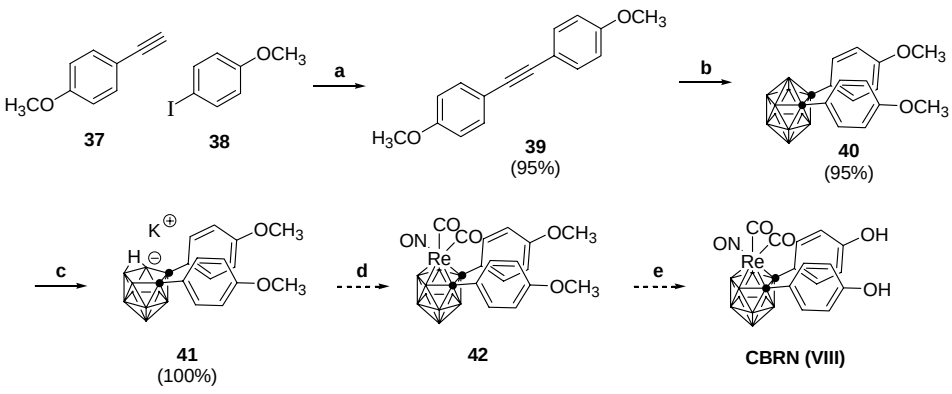
The lipophilic character of the estrogen receptor, coupled with the lipophilic nature of *closo*-carboranes make them attractive scaffolds upon which to build ER ligands. Indeed, work is this field by Endo[3-5] has produced a number of carborane-based ER ligands with good binding affinity (See Figure 2). Radiolabeling under aqueous conditions produces an anionic tricarbonyl species.[6] Use of a di-cationic rhenium-nitroso-dicarbonyl to balance the charge[7-9] provides the potential for a neutral metallocarborane, capable of binding to the estrogen receptor. To test this hypothesis, Sonogashira coupling of methoxyphenyl acetylene **37** with iodoanisole **38** provides the bis-methoxyphenyl acetylene, which is refluxed with decaborane to form the *ortho-closo*-carborane **40**. The *closo*-carborane is degraded to the *nido*-carborane potassium salt, using potassium hydroxide. A *nido*-carborane can be metallated with rhenium tricarbonyl, followed by treatment with a nitrosonium salt to provide the neutral nitroso dicarbonyl complex **42**. Deprotection under Lewis acidic conditions will provide the test compound **CBRN (VIII)**.



ERa RBA = 48%

Figure 3. BE361

Scheme 9

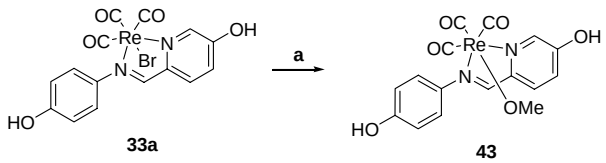


(a) $Pd(PPH_3)_4$, CUI, TEA, ACN, RT, 3h. (b) $B_{10}H_{14}$, Et_2S, Pr_2O, reflux, 12h. (c) ethanolic KOH, RT, 18h. (d) $KF_{(aq)}$, MeOH, 85° C, 1 h. ii. $[NEt_4]_2[Re(CO)_3Br_3]$. 85° C, 12h. iii. $NOBF_4$. (e) BBr_3, CH_2Cl_2, -78° - RT.

Task C Step 2

The second twelve months of support described in this report includes the beginning of those steps described as Task C. Of those, Step 2, the synthesis the methoxy analog of bromide substituted PIRB, PIRM, has been initiated. Conversion of **ADHH** (**33a)** to the methoxy compound proceeds successfully, according to initial NMR spectroscopy experiments. To date, the high polarity of the resulting methoxy complex has complicated final purification of methoxy complex **43**. Future plans include the use of reverse phase HPLC, followed by characterization and binding affinity studies.

Scheme 10



(a) MeOH, NaOH, RT, 1 h.

Key Research Accomplishments

- Key cyclization of 1,3 substituted cyclopentenone accomplished for Task B, step 1 .
- Synthesis of a small library of PIRB ligands accomplished for Task B, step 2. Lead compound is ADHH with RBA to ERα of 2.3%.
- Progress in Task C, step 2 includes synthesis of crude ADHH methoxy analog which is awaiting purification.
- Progress in Task C, step 4 includes the synthesis of radiolabeling-precursor for **CBRN (VIII)**.

Reportable Outcomes

- Poster Presentation **Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor (ER) Ligands for ER+ Tumor Imaging**, at the Era of Hope Meeting, Philadelphia, Pennsylvania, June 8-11th, 2005.
- Poster Presentation **Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor (ER) Ligands for ER+ Tumor Imaging**[10], at the International Symposium on Radiopharmaceutical Chemistry in Iowa City, Iowa, June 24-28, 2005.

Conclusions

Research progress is on schedule with the completion of the Task A, and progress in Task B, a library of **PIRB** ligands, and the key cyclization for the synthesis of **PyCR**. Future plans include pyridyl cuprate addition to a reactive enone, followed by several well-precedented steps to complete the synthesis of **PyCR**. This will complete Task B. Task C has been initiated with the synthesis of a **PIRM** ligand, and a labeling precursor for **CBRN**. Synthesis of **PyCR** analogs, as part of Task C, will proceed using the same synthetic scheme outlined for **PyCR**. Also included in future plans for Task C is the hydration of the alkynyl substituent on triarylpropynylcyclopentadiene **12b** to provide ketone **13b**, a ligand with potential for aqueous labeling to produce **ACR (IV).**

Abbreviations

ACR	1-acetyl-2,3,5-tris-(4-methoxyphenyl)-cyclopentadienylrhenium(I) tricarbonyl **(IV)**
ACT	1-acetyl-2,3,5-tris-(4-methoxyphenyl)-cyclopentadienyltechnetium(I) tricarbonyl **(V)**
ER	Estrogen Receptor
ER+	Estrogen Receptor Positive
ER-	Estrogen Receptor Negative
CBRN	(3)-1,2-bis-(4-hydroxyphenyl)-1,2-dicarbadodecahydroundecaborate (-2) nitroso rhenium dicarbonyl
PyCR	η^1,η^5-1 -(4-hydroxyphenyl)-3-pyridylmethylcyclopentadienyl rhenium(I) dicarbonyl **(II)**
PIRB	{Bromo[*N*-(2-pyridinylmethylene)-4-hydroxyphenylamine]rhenium(I) tricarbonyl}
PIRM	{Methoxy[*N*-(2-pyridinylmethylene)-4-hydroxyphenylamine]rhenium(I) tricarbonyl}
RBA	Relative Binding Affinity

References

(1) Nadal, M. L.; Bosch, J.; Vila Josep, M.; Klein, G.; Ricart, S.; Moreto Josep, M. The Ni-mediated cyclocarbonylation of allyl halides and alkynes made catalytic. Evidence supporting the involvement of pseudoradical Ni(i) species in the mechanism. *J. Am. Chem. Soc.* **2005**, *127*, 10476-7.

(2) Ichikawa, J.; Fujiwara, M.; Miyazaki, S.; Ikemoto, M.; Okauchi, T.; Minami, T. Regioselective Nucleophilic Additions to Cross-Conjugated Dienone System Bearing b-Fluorine: A Versatile Approach to Highly Substituted 2-Cyclopentenones. *Organic Letters* **2001**, *3*, 2345-2348.
(3) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Inada, M.; Kubo, A.; Itai, A. Potent estrogen agonists based on carborane as a hydrophobic skeletal structure: a new medicinal application of boron clusters. *Chemistry & Biology* **2001**, *8*, 341-355.
(4) Endo, Y.; Yoshimi, T.; Iijima, T.; Yamakoshi, Y. Estrogenic antagonists bearing dicarba-closo-dodecaborane as a hydrophobic pharmacophore. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3387-3392.
(5) Endo, Y.; Yoshimi, T.; Miyaura, C. Boron clusters for medicinal drug design: Selective estrogen receptor modulators bearing carborane. *Pure Appl. Chem.* **2003**, *75*, 1197-1205.
(6) Sogbein, O. O.; Merdy, P.; Morel, P.; Valliant, J. F. Preparation of Re(I)- and 99mTc(I)-Metallocarboranes in Water under Weakly Basic Reaction Conditions. *Inorg. Chem.* **2004**, *43*, 3032-3034.
(7) Marti, N.; Spingler, B.; Breher, F.; Schibli, R. Comparative Studies of Substitution Reactions of Rhenium(I) Dicarbonyl-Nitrosyl and Tricarbonyl Complexes in Aqueous Media. *Inorg. Chem.* **2005**, *44*, 6082-6091.
(8) Schibli, R.; Marti, N.; Maurer, P.; Spingler, B.; Lehaire, M.-L.; Gramlich, V.; Barnes, C. L. Syntheses and Characterization of Dicarbonyl-Nitrosyl Complexes of Technetium(I) and Rhenium(I) in Aqueous Media: Spectroscopic, Structural, and DFT Analyses. *Inorg. Chem.* **2005**, *44*, 683-690.
(9) Rattat, D.; Verbruggen, A.; Berke, H.; Alberto, R. Exploring the nitrosyl-approach: \"Re(CO)2(NO)\"- and \"Tc(CO)2(NO)\"-complexes provide new pathways for bioorganometallic chemistry. *J. Organomet. Chem.* **2004**, *689*, 4833-4836.
(10) Ackroyd, N., C.; Katzenellenbogen John, A. Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor (ER) Ligands for ER+ Tumor Imaging. *J. Labelled Compd. Radiopharm.* **2005**, *48*, S243.